

# TOP Journal Club

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## Effect of cilostazol on impaired vasodilatory response of the brachial artery to ischemia in smokers.

Reference: J Atheroscler Thromb 2003;10(2):93-8

The vascular endothelial function of smokers is known to be impaired. This study investigated whether cilostazol could improve the vasodilatory response of the brachial artery to ischemia, an indicator of endothelial function, in ten male smokers. Endothelium-dependent vasodilatation and endothelium-independent vasodilatation of the brachial artery were measured in 11 male non-smokers and 20 male smokers with matching age and weight. The results showed that the vasodilatory response to reactive hyperemia was significantly smaller in the smokers (4.8 +/- 1.6%) when compared to that in the non-smokers (7.6 +/- 2.5%) ( $p = 0.0013$ ). However, no significant difference in the vasodilatory response to isosorbide dinitrate was observed between the two groups. In addition, there were no significant differences in serum lipid, Lp (a), or blood homocysteine between the smokers and non-smokers. When 150 mg/day of cilostazol was administered for two weeks, the vasodilatory response to reactive hyperemia significantly improved (4.2 +/- 1.2% to 7.8 +/- 3.5%,  $p = 0.0032$ ). The increased vasodilatory response to reactive hyperemia by cilostazol was reduced after cessation of the drug (4.5 +/- 1.5%). These findings suggest that cilostazol improves vascular endothelial dysfunction in smokers.

## Pharmacotherapy as adjunctive treatment for serious foot wounds in the patient with diabetes: a case study.

Reference: Ostomy Wound Manage 2003 Apr;49(4):52-5

Chronic foot wounds in patients with diabetes present significant treatment challenges. A 54-year-old woman with type 2 diabetes and two wounds (one on the left great toe and the other on the left medial plantar surface) visited the clinic after the chronic wounds failed to respond to treatment such as hydrotherapy. Subsequent comprehensive care, including debridement; opening tunnels distal, proximal, and medial from the plantar wound; application of a growth factor-stimulant; and treatment with cilostazol to improve both macro- and

microvascular circulation provided excellent wound healing. Amputation was avoided and the patient returned to her regular routine within 6 months. Pharmacotherapy may provide new adjunctive therapy options in the treatment of chronic foot wounds in patients with diabetes mellitus. Controlled clinical studies to ascertain the effects of this treatment are warranted.

## Cilostazol: An "Intermittent Claudication" Remedy for the Management of Third-Degree AV Block

Reference: *Chest*. 2003;123:979-982

Third-degree AV block (3DAVB) of a persistent and not potentially reversible type associated with symptomatic bradycardia is a class I (beneficial, useful, and effective) indication to implant a permanent pacemaker (PP).

Large experience with this procedure and phenomenal technological advances in the pacemaker generators, pacing leads, and programmability of these devices have established this mode of therapy as the "gold standard" to be implemented with almost no exception. Although such a recommendation is provided in the guidelines, it is also stated that alternative therapies can be considered if in the judgment of the physician this is deemed appropriate and/or the patient wishes not to undergo a device implantation. Occasionally, debilitation or incompetence of the patient, serious comorbidities, short expected survival, or involvement of the patients' relatives lead to a decision not to implant a device. Also, for patients destined to undergo the procedure, some patient- or health system-dependent delays are often unavoidable (*ie*, the patient is anticoagulated or febrile, arrangements with the implanting physician or operating room had to be cancelled, or the implantation was unsuccessful). Thus, for such a seemingly straightforward therapeutic recommendation as the implantation of a PP for 3DAVB, it is sobering even for seasoned clinicians to experience the chain of events/actions often interspersed between diagnosis and implantation of the pacemaker. This latent period, up to a point, is useful for many reasons: (1) the diagnosis needs to be established, (2) the permanent or reversible (partially or completely) nature of the conduction abnormality should be determined, (3) the association of symptoms should be sought and managed, (4) the patient must be prepared, and (5) arrangements for PP implantation must be made.

A class of agents known as phosphodiesterase (PDE) inhibitors has also been studied in the management of bradyarrhythmias and AV conduction abnormalities. PDEs are a group of catalytic enzymes that play a wide role in many cellular processes. Xanthines are a type of PDE inhibitors, and examples of PDE type III inhibitors are the drugs amrinone and milrinone. PDE III inhibitors exert their effects by preventing cyclic adenosine monophosphate (cAMP) breakdown, while  $\beta$ -agonists act by increasing cAMP production. Amrinone and milrinone have been employed in the critical care environment for patients with decompensated CHF, but they have led to decreased survival with long-term administration in patients with CHF. Amrinone has increased the ventricular response of atrial flutter in a canine model, suggesting facilitation of AV conduction. Also, in clinical studies, amrinone and milrinone was shown to improve conduction in the right atrium and the AV node.

Cilostazol, a quinolinole derivative with PDE III inhibitory action was introduced 14 years ago in Japan and 3 years ago in the United States as an antiplatelet/antithrombotic agent for the symptomatic management of patients with arterial occlusive disease and **intermittent claudication**. Vast literature exists on the effects of this drug on platelets, various vascular beds and organs, and their blood flows, and its therapeutic role in cardiac diseases, stroke, and management of patients who have undergone percutaneous coronary interventions, including "stenting. The pharmacokinetics, pharmacodynamics, safety, and side effects of single doses, short-term, and long-term administration have been extensively studied. It has been found that cilostazol exerts positive chronotropic and dromotropic effects resulting in increased heart rates in patients with sick sinus syndrome, atrial fibrillation, and Mobitz I second-degree (Wenckebach) AV block. The positive chronotropic effect of the drug has been clearly demonstrated, and the dromotropic effect was shown by the increase in ventricular response of patients with atrial fibrillation; however, the Mobitz I second-degree AV block persisted. This experience has set the stage for evaluating the effect of cilostazol in patients with 3DAVB.

Physicians could start administering cilostazol to carefully selected patients with 3DAVB. However the heart rate of patients under treatment should be checked both at rest and following the routine tasks elderly patients engage in to appreciate adequacy of the escape ventricular activity, and whether ventricular ectopy has arisen. Occasional long-term ambulatory ECG monitoring sessions could provide more substantial data on these, and also resolve whether cilostazol results in meaningfully prolonged

intervals of returned AV synchrony. Also it is important that this therapy is assessed in reference to its long-term contribution in the patient's lifestyle, as compared with how the patients fared prior to acquiring 3DAVB. Cilostazol, like other PDE III inhibitors, should be avoided in patients with CHF or left ventricular dysfunction; four patients in the study were in class III, and possible progression to class IV status should be kept in mind. Finally drug interactions (known and emerging) of cilostazol should be reviewed and followed, as other medications are added to the patients' regimens; a case in point is the co-administration of cilostazol and clopidogrel (the latter recommended for primary and secondary prevention of stroke), which is currently undergoing evaluation. Other such interactions may prove advantageous like the combined use of cilostazol and  $\beta$ -agonists or adenosine receptor antagonists, as in the case of the three patients in the study who did not receive a PP. There are no data as to what prompts the delays often encountered in the permanent management of 3DAVB in many patients; perhaps this may be due to uncertainty about the permanency of the conduction abnormality on the part of the clinician, ambivalence/procrastination in the patient or relatives to agree with the procedure, or unavailability of local expertise to implant the device. In any case, it is reassuring to have an addition in the pharmacologic armamentarium available for the management of patients with 3DAVB. More research on this topic and clinical use of cilostazol will clarify its role in the stabilization of the bulk of patients awaiting implantation of a PP, and clinical amelioration and improved lifestyle for those in the minority who do not undergo such a procedure. It is in the context of all of the above that this early experience with cilostazol in patients with 3DAVB constitutes an advancement.

### **Effect of oral supplementation with branched-chain amino acid granules on serum albumin level in the early stage of cirrhosis: a randomized pilot trial.**

Early oral supplementation of BCAA for HCV-related cirrhosis with serum albumin level between 3.5 and 3.9 g/dl and Branched chain amino acids and Tyrosine Ratio (BTR) less than 4.0, improves serum albumin levels and thus might improve prognosis.

*Reference: Hepatol Res 2003 Mar;25(3):312-318*

<http://www.thai-otsuka.co.th/pxnews/index.html> Opinions and suggestions are welcomed Dr. Shwe Win, [shwewin@thai-otsuka.co.th](mailto:shwewin@thai-otsuka.co.th)